PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

THORESEN, Liv-Heidi
Amersham Health AS
Nycoveien 1-2
P.O. Box 4220 Nydalen
N-0401 Oslo
NORVEGE

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25 APR 2005
LHT
Patent Dep. Oslo

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	20.04.2005
Applicant's or agent's file reference PN0273-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NO 03/00444	29.12.2003	30.12.2002

Applicant
AMERSHAM HEALTH AS et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

DUE DATE:	
FORMALITIES:	MN
PAT. OFF:	LHT V
ON DB:	26-Apr-2005
CASE NO:	PN0273-PCT

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer
Evers, A
Tel. +49 89 2399-7061

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PN0273-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/NO 03/00444	International filing date *(day/month/year)* 29.12.2003	Priority date *(day/month/year)* 30.12.2002
International Patent Classification (IPC) or both national classification and IPC C07K2/00		
Applicant AMERSHAM HEALTH AS et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05.07.2004	20.04.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Fausti, S Telephone No. +49 89 2399-7389

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NO 03/00444

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-17	as originally filed

Claims, Numbers

2 (part), 3-10	as originally filed
1, 2 (part)	filed with telefax on 05.04.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1, 3-10 (partially)

   because:

   ☒ the said international application, or the said claims Nos. 10 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1, 3-10 (partially)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

N.1 The subject-matter of claims 1, 3-10 has been searched only in so far as it relates to the peptides defined with formula II and to the peptides of Seq. IDs 1-14 (as disclosed in claim 2 and examples 1-3). Accordingly, the examination will be limited by considering that the scope of the claims is restricted to the searched subject-matter (Rule 66.1(e) PCT).

N.2 Claim 10 relates to a diagnostic method carried out on the human/animal body. Such a method is considered to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. DOCUMENTS.

Reference is made to the following documents:

D1: WO 01/52875 A;
D2: WO 99/40947 A;
D3: WO 01/57226 A;
D4: WO 97/02479 A;
D5: US 5981229;
D6: WO 99/14321 A;
D7: US 5948667;
D8: WO 99/10498 A;
D9: EL-SHEIKH AMR ET AL., CANCER RESEARCH (2002) vol. 62, no. 23, pages 7118-7123;
D10: US 2002/114780 A;

D11: WO 03/007689 A;
D12: WO 03/074005 A.

1.1 D1 discloses disulphide-cyclic peptides from growth factor proteins modulating the activity of the growth factor, e.g. VEGF-D, for use as angiogenesis inhibiting agents in therapy or in labelled forms for diagnostic purposes (see: from line 10 on page 19 to line 30 on page 20; page 26, lines 1-19; page 32, table 1).

1.2 D2 discloses peptides binding to a VEGF receptor for targeting sites of angiogenesis with diagnostic or therapeutic agents (see: abstract; pages 12-13; examples 2, 5 and 6; claims 1 and 3).

1.3 D3 discloses antibodies, or fragments thereof, which bind to a CC-chemokine receptor and inhibit chemokine signalling, for use as therapeutic and/or diagnostic agents against inflammatory disorders and HIV infections (see the CA abstract and figure 14 of D3).

1.4 D4 discloses anti-tumour antibodies for diagnostic and therapeutic purposes (see abstract and particularly the V_H fragment of Seq. ID 48).

1.5 D5 discloses proteins from Gram-positive bacteria and vaccines thereof (see abstract and the protein of Seq. ID 58).

1.6 D6 relates to apoptosis-regulating proteins and agents modulating this protein activity for therapeutic, diagnostic and screening purposes (see abstract and the protein of Seq. ID 6).

1.7 D7 discloses a xylanase enzyme for the preparation of feed supplements (see abstract and the protein of Seq. ID 2).

1.8 D8 discloses enzymes involved in the lignin biosynthesis (see abstract and the protein of Seq. ID 11).

1.9 D9 and D10 disclose the heparin binding domain of VEGF as a target for the delivery of therapeutic agents to tumour tissues (see the abstracts). In particular, D10

discloses antibodies against said VEGF domain.

2. CLARITY and SUPPORT (Art. 6 PCT).

2.1 The International Examination Authority agrees with the observations made by the Search Authority with respect to lack of support and disclosure (Art. 5 PCT) for the peptides of formula I (see Box I.2 of the International Search Report).

2.1[a] Despite the peptide length is limited from 9 to 21 amino acid residues, formula I does not appear to specifically define any relevant peptide motif, which could account for the desired peptide binding properties, in view of the broad range of values of the variables Z^1, X^1-X^5, X^7-X^9 and Z^2. In particular, more than 103'680 different peptide motifs fall within the definition of formula I, whereas the application provides experimental data of biological activity only for one of them (see examples 1-3).

2.2 Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim defines the residues Z^1 and Z^2 in terms of their amino acid structure and a desired chemical property, namely the possibility to form disulphide bonds. In the case of Z^1, the claim also refers to generic residues, for which no structural feature is provided (except for a preferred, but not limiting, embodiment). As it is only based on the desired chemical property, the definition of the generic Z^1 residue is unclear. Moreover, the claim does not provide any indication of the reaction conditions under which the disulphide bond is formed, and therefore a broad range of suitable functional groups could be introduced on the generic Z^1 residue in order to form the desired bond. Accordingly, the definition of the generic Z^1 residue is not limiting the claimed scope.

2.3 Claim 7 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved, namely the possibility of carrying a multiplicity of vectors (see "...can carry a multiplicity of vectors..."), without providing the technical features necessary for achieving this result. These technical features, i.e. one or more linker moieties, are only defined in the description (see page 6, third paragraph), contrary to the PCT requirements (see PCT Guidelines 5.10).

3. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT).

3.1 Claims 1-9 relate to pharmaceutical compounds and their pharmaceutical compositions, which can be made in the pharmaceutical industry. Hence, the subject-matter of these claims is to be considered industrially applicable according to article 33(4) PCT.

3.2 For the assessment of the present claims 10 on the question whether it relates to subject-matter having an industrial application, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. NOVELTY (Art. 33(2) PCT) and INVENTIVE STEP (Art. 33(3) PCT).

The following conclusions are based on a restricted scope of the claims, which only include the searched subject-matter (see point N.1 above).

4.1 The subject-matter of claims 1 and 2 is novel because the prior art does not disclose any peptide having a sequence length of maximum 21 residues and an amino acid sequence according to formula II, nor a peptide as defined in claim 2.

4.1[a] In particular, the short VEGF-binding peptides disclosed in D1 and the VEGF receptor-binding peptides disclosed in D2 differ in the amino acid sequence (see points 1.1 and 1.2 above).

4.1[b] The antibody fragments and the proteins disclosed in D3-D8 differ in that they have a longer amino acid sequence (see points 1.3-1.8 above). In addition, the short peptide fragments of the preferred embodiments of D3 (see claim 8) have amino acid sequences, which do not fall within formula II and differ from the ones of claim 2.

4.1[d] D9 and D10 are concerned with the structure of the heparin-binding domain of VEGF, to which the claimed peptides should bind, and do not disclose any short peptide of relevant amino acid sequence.

4.2 D1 and D2 can be independently considered to represent the relevant state of the art because these documents disclose short peptides, which bind to VEGF or to the VEGF receptor and modulate the activity of this growth factor, for use as angiogenesis inhibitors in therapy or diagnosis (see points 1.1 and 1.2 above).

4.2[a] The problem to be solved can therefore be regarded as the provision of alternative peptides with angiogenesis inhibitory activity for pharmaceutical uses.

4.2[c] The solution proposed consists in the 9-21 amino acid long peptides defined in claim 1 by means of formula II and in claim 2. The pharmaceutical activity of these peptides is based on the fact that they specifically bind to the heparin-binding domain of VEGF. Despite this VEGF domain has been suggested as a therapeutically relevant target (see point 1.9 above), no short peptide binding thereto has been disclosed. The solution proposed involves an inventive step because it has not been suggested and cannot be derived from the prior art. Irrespective of the specific binding properties of the peptides, it is also noted that the amino acid sequences of the claimed peptides are not homologous to the ones of the VEGF-modulating peptides disclosed in D1 and D2.

4.3 The subject-matter of claims 3-10 is novel and involve an inventive step over the available prior art because these claims relate to: (i) diagnostic and therapeutically active agents, (ii) pharmaceutical compositions and (iii) medical uses comprising/involving the peptides of claim 1 and 2.